Optimizing Nutrition Delivery in Critically Ill Patients on Vasopressors

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KEYWORDS

• Vasopressors • Norepinephrine • Enteral nutrition • Critical illness • Nutrition
• Septic shock • Intensive care unit

KEY POINTS

- Trophic EN provides gut-protective, non-nutritional benefits in shock, helping prevent dysbiosis, preserve barrier integrity, enhance vagal anti-inflammatory signaling, and reduce toxic mesenteric lymph effects.
- Early trophic EN after resuscitation may improve outcomes and lower mortality on low–moderate norepinephrine; full-dose EN on higher vasopressors increases GI complications.
- When starting Early EN, Resuscitation First- Initiate EN only when lactate is falling, vasopressor doses are stable or falling, and fluid requirements have plateaued.
- Start small: Use gastric trophic feeds (10–20 mL/h) only while on vasopressors—avoid post-pyloric feeding in shock. "Trophic-first/less is more"; consider elemental formulas.
- Monitor closely: Stop EN for intolerance—check GRVs (hold if >500 mL), abdominal distension or pain, and rising lactate while feeding on vasopressors.

WHY THE INTESTINE MATTERS IN CRITICAL ILLNESS—AND WHY FEEDING IT EARLY CAN HELP

For decades, the intestinal tract has been framed as a central driver of the trajectory of critical illness—frequently described as the *motor of systemic inflammation and organ failure*.[1,2] Perturbations in epithelial homeostasis during severe illness can heighten proinflammatory cytokine signaling,[3] weaken barrier integrity,[4–6] and accelerate programmed cell death,[7–10] collectively contributing to multiple organ failure (MOF). As shown in **Fig. 1**, these derangements are fueled by a rapid loss of microbiome diversity (dysbiosis),[11] changes in permeability,[1,2] maladaptive neuroimmune signaling via the vagus nerve,[12] and generation of pathologic mediators in mesenteric lymph,[13,14]

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Abbreviations	
CI	confidence interval
EE	energy expenditure
EN	enteral nutrition
GRV	gastric residual volume
LEN	and late enteral nutrition
MOF	multiple organ failure
NOBN	nonocclusive bowel necrosis

which further propagate systemic inflammation, driving downstream organ injury. Ultimately, both immediate and longer term outcomes hinge on the timely provision of nutrients that enable recovery.[15–17]

To counter the gut's role as an amplifier of inflammation and MOF, several interventions have been explored. Among them, early trophic enteral nutrition (EN) exerts non-nutritional benefits in shock to attenuate systemic inflammation and MOF including (1) Preventing dysbiosis, (2) Maintaining gut-barrier function; (3) Improved vagus nerve signaling to reduce systemic inflammation; and (4) Preventing toxicity of mesenteric lymph. Beyond macronutrient delivery, these key non-nutritional effects of EN are well-described in existing literature-including evidence for preserving mucosal structure and function and limiting hyper-permeability[5]; dampening oxidative stress and maladaptive inflammatory responses while maintaining humoral immunity[5]; and improving metabolic efficiency by reducing insulin resistance.[3] Starvation, absence of luminal nutrients and prebiotics, and exposure to endogenous/exogenous catecholamines, which can promote microbiome dysbiosis.[11,18] Even partial enteral feeding ($\sim$ 20% of requirements) can preserve the microbiome, gut barrier function, and elements of innate immunity.[19] Mechanistically, EN can activate anti-inflammatory vagal–cholinergic pathways via cholecystokinin (CCK)-mediated signaling in shock states,[12,18] thereby reducing permeability, inflammatory tone, and bacterial translocation.

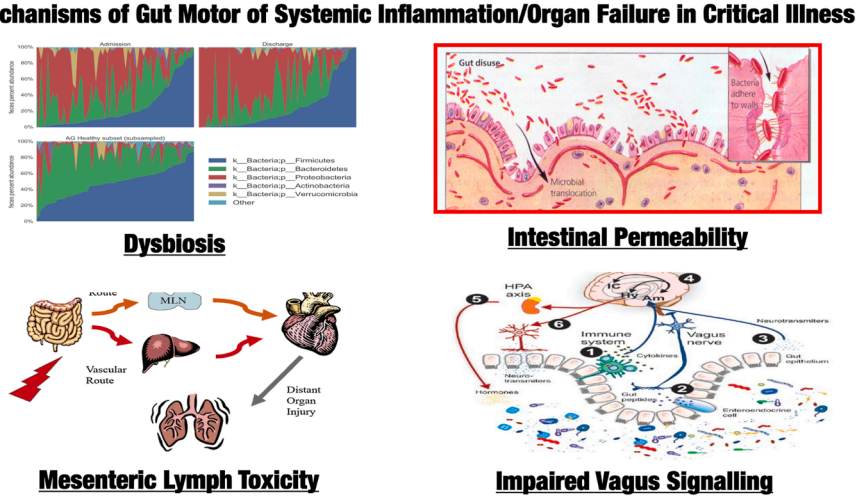

Fig. 1. Mechanisms of gut motor of systemic inflammation/organ failure in critical illness thought to be influenced and attenuated by early EN. Key references.[58–61]

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Feeding, Perfusion, and the Splanchnic Circulation Under Vasopressors

Experimental models have long documented that EN can improve splanchnic perfusion in sepsis and shock.[20,21] Human data in cardiogenic shock demonstrate that EN can raise cardiac index, increase splanchnic blood flow, and preserve intestinal absorptive capacity—even during vasopressor administration.[22,23] Despite these signals, clinicians remain appropriately concerned that early EN in vasopressor-dependent shock could precipitate mesenteric ischemia or nonocclusive bowel necrosis (NOBN)—patchy, segmental ischemia possibly triggered by mucosal hypoxia and/or increased oxygen demand from feeding.[24] All vasopressors can potentially impair gastrointestinal perfusion: if EN augments mucosal oxygen consumption when delivery is limited, ischemia may ensue. Notably, much of this concern traces to animal work employing arterial occlusion before EN and to pathology from atherosclerotic occlusive mesenteric disease—not necessarily representative of distributive shock under modern intensive care unit (ICU) care.[25]

Vasopressors are not equal in their gut effects, and dose clearly matters. In critically ill patients, rising catecholamine exposure correlates with higher intestinal fatty-acid binding protein (marker of mucosal injury), higher lactate, and increased 28-day mortality.[26] Porcine sepsis studies show epinephrine impairs microvascular flow and causes early mucosal injury,[27] whereas norepinephrine findings are mixed.[27,28] Phenylephrine in peritonitis increased blood flow to the jejunal muscularis without changing splanchnic oxygen extraction.[27] Vasopressin has been linked to rectosigmoid ischemia during cardiopulmonary bypass,[29] yet under some conditions may mitigate cardiopulmonary bypass (CPB)-related jejunal microcirculatory disturbances through endothelin-mediated effects.[30]

Human studies echo these nuances. In septic shock, patients receiving epinephrine (vs norepinephrine $\pm$ dobutamine) had lower splanchnic blood flow and oxygen consumption, higher lactate, and lower gastric pH despite similar systemic hemodynamics.[31] In a small cardiothoracic (CT)-ICU trial, phenylephrine and norepinephrine both increased systemic vascular resistance (SVR) and mean arterial pressure (MAP) without altering cardiac index; phenylephrine raised splanchnic oxygen extraction with no difference in jejunal perfusion.[32] Multiple investigations associate vasopressin with gastric and enteric hypoperfusion in septic shock.[24] Of note, EN-related mesenteric ischemia is most frequently described in trauma, burn, and surgical populations fed via jejunostomy.[33]

Guideline Perspective and Practical Warning Signs

Contemporary Society of Critical Care (SCCM)/American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines advise withholding EN during hemodynamic compromise until the patient has been adequately resuscitated and stabilized, and then cautiously initiating or resuming EN as vasopressor support is reduced, with vigilance for feeding-related bowel ischemia.[34] When NOBN occurs, reported incidence ranges from $\sim$ 0.3% to 8.5% with a strikingly high mortality (46%–100%).[24] Reliable early clinical indicators are limited, but commonly cited warning signs include markedly increased gastric residuals (>500 mL), new abdominal distension or pain, nausea/vomiting, and unexplained lactate elevation coincident with feed initiation/escalation.[24] Many cases emerge later in the feeding course rather than immediately after initial resuscitation, suggesting occult mucosal hypoperfusion can persist despite acceptable systemic parameters.[24] Judicious fluid strategies—especially avoiding crystalloid over-resuscitation—may limit bowel edema and help gut perfusion.[35]

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More recent guidelines include The Surviving Sepsis Campaign 2021, which issues a weak recommendation to start enteral nutrition within 72 hours in sepsis/septic shock, citing low-quality evidence that favors physiologic plausibility over proven mortality benefit.[36] ASPEN guidance (2022) notes that initiating EN within 48 hours may improve tolerance in septic patients on vasopressors—one study reported 78% tolerance with early initiation versus 48% when delayed ($P = .015$)—while emphasizing that high-dose EN is not recommended in unstable shock.[37]

Clinical Evidence: How to Feed Safely on Vasopressors

A growing body of clinical work supports the feasibility and benefit of early EN during vasopressor therapy, while clarifying doses and strategies that promote safety and potentially reduced mortality. In a pivotal retrospective cohort, early EN in ventilated ICU patients on vasopressors was associated with lower hospital mortality after multivariable adjustment, with those on multiple vasopressors appearing to benefit most.[38] In septic shock, trophic EN (<600 kcal/day, ~ 20 mL/h) correlated with shorter ICU stay and fewer ventilator days compared with full-dose EN or no EN after adjustment.[39] Tolerance data show ~ 75% of EN attempts succeed under vasopressors, with intolerance linked to higher norepinephrine dose and to the choice of agents.[40] Cardiothoracic ICU series suggest EN is feasible and safe even in severe circulatory failure, though nutrition goals are often not fully achieved.[41] A key large health outcomes study demonstrated the safety and clinical outcome benefit of early EN delivery on vasopressors. The observational study compared outcomes between early EN and late enteral nutrition (LEN) in ventilated patients with shock requiring low-(<0.1 ug/kg/min), medium-(0.1–0.3 ug/kg/min), or high-dose (>0.3 ug/kg/min) norepinephrine-delivery.[42] About 52,563 patients were identified as meeting entry criteria. The 28-day mortality rate was observed to be significantly lower in the early EN versus LEN group in the low-dose norepinephrine group (risk difference, 2.9%; 95% confidence interval [CI], 4.5%–1.3%) and the medium-dose norepinephrine group (risk difference, 6.8%; 95% CI, 9.6%–4.0%). The high-dose norepinephrine group did not demonstrate a significant difference between the early EN and LEN groups (absolute risk difference, 1.4%; 95% CI, 7.4%–4.7%). The authors conclude that data suggest that early enteral nutrition (EEN) is associated with a reduction in mortality in ventilated adults treated with low-dose or medium-dose noradrenaline but not in those requiring high-dose norepinephrine, although the size of the high-dose norepinephrine subgroup may have been too small to demonstrate significant differences.[42]

Major Randomized Controlled Trials

The largest randomized controlled trial (RCT) to date—NUTRIREA-2 (2018)—randomized 2410 ventilated adults with shock to early EN versus early parenteral nutrition (PN) and and found no difference in 28-day mortality (37% vs 35%, $P = .33$), but higher gastrointestinal complications with early EN: vomiting (34% vs 20%), diarrhea (36% vs 33%), bowel ischemia (2% vs <1%), and acute colonic pseudo-obstruction (1% vs <1%).[43] It is important to note that the average starting norepinephrine dose in this study was quite high than in other early nutrition trials. The mean entry norepinephrine dose of 0.53 μg/kg/min is a dose that is higher than the exclusion limits for other similar large contemporary nutrition RCTs (including PermiT and EDEN trials).

Effect Modification by Vasopressor Dose

The aforementioned large Japanese database study (n = 52,563) showed dose-dependent effects: early EN reduced 28-day mortality at low (<0.1 μg/kg/min) and

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medium (0.1–0.3 μg/kg/min) norepinephrine doses, but offered no benefit at high doses (≥0.3 μg/kg/min).[42]

Effect Modification by Shock Duration

A 2025 secondary analysis of a cluster-randomized trial (n = 785) found that in transient shock (resolution within 24 hours), early EN was associated with lower odds of organ failure or mortality (adjusted OR 0.63, 95% CI 0.41–0.95, $P = .027$); in persistent shock, early EN conferred no benefit and trended toward harm (adjusted OR 1.28, 95% CI 0.64–2.58).[44]

Conflicting Recent Evidence

A 2025 MIMIC-IV study (n = 4673) reported that early EN was associated with increased 28-day mortality after inverse probability weighting (adjusted OR 1.80, 95% CI 1.42–2.27), with stronger associations at medium-dose (OR 1.66) and high-dose (OR 1.90) vasopressor strata.[45] In a 2022 nested cohort analysis from an international multicenter trial (n = 626), early EN was associated with more ICU-free days and vasopressor-free days in unadjusted analyses, but these benefits were no longer significant after adjustment for illness severity.[46]

Putting the Evidence Together

Overall, contemporary evidence supports carefully titrated early EN in resuscitated patients on modest vasopressor support, while highlighting heterogeneity driven by vasopressor dose, illness severity, and shock persistence. Guidelines and expert opinion converge on a *less is more* strategy—favoring trophic or low-dose EN in the acute shock phase and avoiding rapid escalation to goal feeds under high-dose catecholamines.[36,37,47] Clinicians should weigh nutrition risk (eg, low-body mass index [BMI] and sarcopenia) and strongly consider supplemental PN to achieve protein/energy targets (only when adequate resuscitation is achieved-see **Table 1**) if full EN is not yet felt to be safe.[48,49] These data underscore the need for validated bedside tools or biomarkers to guide EN initiation and advancement in vasopressor-dependent shock; until such tools exist, vigilance for early intolerance signals and dose-aware feeding protocols remains essential.[44–47]

Practical Suggestions for Feeding on Vasopressors

Practical clinical guidance for safety and optimal EN delivery in ICU patients receiving vasopressors is summarized in **Table 1**. I think a few key guidelines that should be followed, given the existing data are (1) Only feed the stomach (not small bowel or post-pyloric feeding) in patients on vasopressors so that an accurate assessment of gastrointestinal (GI) tolerance can be made; (2) Check gastric residual volumes (GRVs) routinely in patients being fed on vasopressors. While recent data and guidelines suggest that in medical ICU patients, GRV assessment does not improve outcome, I would advocate in patients on vasopressors GRV assessment is warranted with a cut-off of greater than 500 cc used for stopping EN delivery; and (3) Any patient exhibiting signs of feeding intolerance (as described in **Table 1**) and all patients who are not fully resuscitated should not receive EN until the patient is adequately resuscitated.

The fundamental clinical challenge we face is the absence of validated bedside tools to guide EN initiation and advancement in vasopressor-dependent shock.[47,50] Clinicians must balance gut-protective benefits of EN against risks of intolerance/ischemia by integrating vasopressor dose, EN dose, and illness severity—decisions currently made without objective guidance.[47] Urgent research should develop and

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Table 1
Practical evidence-based approach to enteral nutrition feeding and nutrition delivery in ICU patients on vasopressors

Vasopressor Choice	Vasopressor Dose	Resuscitation Markers and Suggestions for Enteral Nutrition Delivery Safety	Feeding Strategy	Signs of Intolerance
Safest for gut blood flow and EN tolerance: Norepinephrine, norepinephrine/dobutamine, and phenylephrine > epinephrine > greatest risk of EN feeding on vasopressin/dopamine (Key references:[27,28,31–33,57]).	*Norepinephrine doses (equivalents):* <1.0 μg/kg/min: optimal 1.0–3.0 μg/kg/min: acceptable with caution; >0.5 μg/kg/min: avoid EN—(Key references:[40,41,57]).	1. Lactate normalized or falling rapidly 2. Vasopressor dose decreasing or stable 3. Mixed Venous 02—within normal limits (WNL) or elevated 4. Fluid requirements stabilizing, no ongoing active bleeding 5. Limit crystalloid fluid over-resuscitation to reduce bowel edema (especially in septic shock—with more pronounced vascular leak) (Key references[34,35,57]).	1. Start with *gastric-only* delivered trophic feeding (10–20 cc/h) (NO postpyloric feeding) 2. Advance EN slowly and watch for signs of intolerance 3. Consider elemental or peptide formula to minimize gut O2 consumption and for improved absorption (Key references[24,34,50,57]).	1. Increased gastric residual (>500 cc) 2. Abdominal distension 3. Nausea/vomiting 4. New abdominal pain 5. Unexplained elevation in lactate with feeding initiation or escalation 6. Intra-abdominal hypertension or abdominal compartment syndrome Key references:[24,57]

Adapted and updated from Reference.[57]

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validate bedside tools and biomarkers to safely steer nutrition therapy in this high-risk population.[50]

Contemporary evidence supports restrictive-dose EN during the acute phase for patients on vasopressors.[47,50] Commentary on NUTRIREA-2 and NUTRIREA-3 notes more GI complications with full-dose EN under high vasopressor support, again reinforcing a *less is more* approach—favoring trophic/low-dose EN (1.0–1.2 kcal/mL) with higher protein and lower fiber during acute shock.[37,47] Shock duration modifies benefit: transient shock is associated with improved outcomes with early EN, whereas persistent shock shows no benefit.[44]

Vasopressor type/dose strongly influences EN tolerance, as described in **Table 1**. Reported tolerance rates vary—phenylephrine (100%), norepinephrine (74.4%), epinephrine (66.4%), dopamine (63.8%), and vasopressin (58.9%).[37] Agents such as dopamine, epinephrine, phenylephrine, and vasopressin typically reduce splanchnic blood flow, whereas inotropes (dobutamine and milrinone) can increase cardiac index and GI perfusion when used independently.[37] ASPEN suggests considering trophic-only feeding or holding EN if vasopressor dose equivalent score greater than 12; initiate within 48 hours of vasopressor start depending on dose, with gastric feeding preferred while on pressors.[37]

Clinical monitoring parameters: As stated earlier, routine gastric residual volume (GRV) checks are not supported by strong evidence; however as emphasized earlier I would advocate checking GRVs in patients on vasopressor to reduce the risk of missing early bowel ischemia or malperfusion. Lactate lacks sufficient evidence as a reliable EN tolerance marker.[37] Primary bedside signals of intolerance remain paramount: vomiting and rising GRV suggest upper GI intolerance; sudden abdominal pain, distension, ileus/paralysis, or increasing intra-abdominal pressure suggest lower GI intolerance—feeding should be stopped if ischemia is suspected.[37,51] Daily plasma phosphate monitoring is recommended to detect refeeding syndrome; a ~30% decline should prompt EN rate reduction and high-dose thiamine.[51]

No widely validated bedside tools or biomarkers currently exist to guide safe initiation and advancement of EN in vasopressor-dependent critical illness, highlighting a major gap.[47,50] Several parameters show promise: the MAP/NE-equivalent (MAP/epinephrine equivalent [NEQ]) index predicted feeding intolerance at a threshold of 417 mm Hg·μg·kg·min measured 6 hours pre-EN with 81% sensitivity and 52.9% specificity (area under curve [AUC] 70.3%; 95% CI 55.1–85.5), outperforming NE dose alone (AUC 65.3%) and NE-equivalents (AUC 66.2%); however, external validation is lacking.[52] Basic hemodynamic cutoffs suggest EN may be reasonable at MAP $\geq$60 mm Hg and held at MAP less than 50 mm Hg, yet these thresholds are based on limited evidence and do not account for individual variability or vasopressor requirements.[37]

We continue to need meaningful randomized controlled data on the effect of early EN delivery on vasopressors as most existing studies are retrospective data or large health outcome database studies. However, the growing body of existing data consistently states that when low-dose EN is delivered to resuscitated patients on low or moderate doses of vasopressors, that safety and potentially improved outcomes can be achieved. This recommendation is timely as recent key guideline papers recommend that early high-dose feeding should be avoided in critically ill until patient is stabilized early in ICU stay.[53,54] Specifically, guidelines recommend hypocaloric nutrition (not exceeding 70% of energy expenditure [EE]) (measured via metabolic cart) should be administered in early phase of acute illness, then after day 3, energy delivery can be increased up to 80% to 100% of measured EE.[53] It is likely that the mechanistic rationale for the hypothesized clinical benefits of early EN

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includes both non-nutrition-related gut protective pathways (Fig. 1) and the early feeding-derived nutritional outcome benefits. One clearer message from the NUTRIREA-2 trial indicates that in severe shock with high (>0.5 ug/kg/min norepinephrine) vasopressor doses, rapid escalation to full EN goal is not safe and should not be practiced. Thus, we must continue to look for improved methods to address the silent epidemic of preexisting malnutrition in critically ill patients-with as many as 1 in 2 (30%–50%) of patients being malnourished at admission to ICU.[55] Further, we must urgently address the ubiquitous and unacceptable starvation that is occurring not just early in ICU patients when they may present with shock, but that we know occurs for greater than 10 days in ICUs worldwide.[56] Thus, it is essential and urgent we look for safe, evidence-based pathways to deliver nutrition via early EN and/or PN rather than tolerating the ongoing iatrogenic starvation of critically ill patients in ICUs worldwide.

CLINICS CARE POINTS

- Early trophic EN after resuscitation may improve outcomes and lower mortality on low–moderate norepinephrine (0-0.3 (ug/kg/m) (micrograms per kilogram per minute); full-dose EN on higher vasopressors increases GI complications.
- Start with trophic gastric feeds (10–20 mL/h) in patients on vasopressors when acute shock is adequately resuscitated to reduce gut ischemia risk—avoid post pyloric feeding while on vasopressors.
- Use a "Less Is More" early feeding strategy, advancing only when hemodynamics improve and vasopressor doses are stable or decreasing.
- Consider elemental or semi elemental formulas to lower digestive workload and intestinal oxygen demand in early shock.
- Monitor closely for intolerance, including rising lactate, abdominal distension, worsening pain, or hemodynamic instability.
- Check gastric residual volumes (GRVs) during vasopressor use; hold feeds for GRV >500 mL or persistent high residuals with symptoms.
- Prioritize perfusion markers (lactate trends, capillary refill, mixed venous oxygen saturations > 70% vasopressor requirements) over static thresholds when deciding whether to continue EN.
- Stop EN immediately with any signs of gut ischemia, including sudden severe abdominal pain, bloody output, or escalating lactate without another explanation.

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